rejections under 35 U.S.C. §§ 112, first and second paragraph, and 103(a). All the pending claims were rejected on new grounds in the Office Action mailed February 25, 2002.

I. REJECTION UNDER § 112, FIRST PARAGRAPH, ENABLEMENT

Claims 39-47, 59, 60 and 72 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Patent Office asserts that the specification enables only plant transformation vectors based on the GVG system, and "does not provide reasonable enablement for vectors comprising all transcription factors and inducible promoter systems and non-plant vectors." Office Action at 3. The Patent Office asserts that it would require "undue experimentation" to determine which inducible promoter systems would be sufficiently "tight" to function in the claimed invention. Office Action at 5. Applicants respectfully submit that this assertion is misplaced.

A. The Legal Standard To Be Applied

The enablement requirement of the first paragraph of § 112 is met if the specification teaches even a single means for carrying out the invention. Engel Industries, Inc. v. Lockformer Co., 20 U.S.P.Q.2d 1300, 1304 (Fed. Cir. 1991) ("The enablement requirement is met if the description enables any mode of making and using the claimed invention."); see also, MPEP § 2164.01(b). Furthermore, an applicant is not required to recite specifically

each and every means of carrying out the invention, so long as the specification provides sufficient guidance to the person of ordinary skill in the art to practice an embodiment of the invention without the need for undue experimentation. United States v. Telectronics, Inc., 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988), cert. denied 490 U.S. 1046 (1989); Spectra-Physics, Inc. v. Coherent, Inc., 3 U.S.P.Q.2d 1737, 1743 (Fed. Cir.), cert. denied 484 U.S. 954 (1987); see also, MPEP § 2164.02 ("Because only an enabling disclosure is required, applicant need not describe all actual embodiments.")

Requiring the present applicants to list each and every inducible promoter system that could function in the claimed invention is an unnecessary and unreasonable burden. The specification teaches specifically how to practice the invention with one specific embodiment, the GVG system, and provides extensive discussion of the criteria required of not only the system as a whole, but the inducible promoter in particular. Examples of other inducible promoter systems are provided. Specification page 5, lines 14-18. The present specification provides ample methodologies and performance criteria to be applied in selecting an appropriate promoter system. A person of ordinary skill in the art would need only routine knowledge to select potential promoters, and only routine experimentation to

determine which promoters would in fact work in the system. The focus of a determination of "undue experimentation" is not the amount of work necessary, but rather the nature of the work necessary:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed."

Ex parte Jackson, 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982). The need for experimentation, even a great deal of experimentation, does not render a specification non-enabling, unless such experimentation would require "ingenuity beyond that to be expected of one of ordinary skill in the art." See In re Angstadt & Griffin, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

B. Failure Of The Evidence

The Patent Office has provided no evidence, and no reasoning beyond a bare assertion, that the type of experimentation required to practice the claimed invention would require knowledge and skill beyond that of the ordinary practitioner in the art, or that it would require any further innovation. It is the burden of the Patent Office to do so:

> "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go through the trouble and expense for supporting his presumptively accurate disclosure.

In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). Absent such evidence or reasoned argument, statements in the specification must be taken as true and correct, and the specification is considered enabled. This principle was settled by the Court of Claims and Patent Appeals over 20 years ago, in the case In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A., 1971):

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirements of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

169 U.S.P.Q. at 369. Application of these standards to the present specification and claims shows that the requirements of the first paragraph of § 112 are fulfilled.

C. Rejection Of Claim 47 Mooted

The Office Action further states in regard to claim 47 that there is no enablement of chloroplast transformation vectors.

Office Action at 6. Such enablement is provided in Example 3 of the specification. However, this rejection has been rendered moot by the cancellation of claim 47.

D. Invention Not Limited To Use In Plants

The Patent Office also asserts that the disclosure of the specification is limited to use in transgenic plants and plant cells. This is not so. All of the elements of the claimed vectors are known to function in organisms other than plants, and there is nothing in the specification to limit the invention solely to use in plants. In fact, the claims as originally filed comprised the use of the claimed vectors in organisms other than plants, as indeed they still do. The Patent Office has presented no evidence or reasoning that would indicate that the claimed vectors would not work in non-plant organisms/cells, as it must do to support an enablement rejection. In re Marzocchi, 160 U.S.P.Q. at 370.

While plants are used to exemplify the invention, a person of ordinary skill in the art would recognize that the invention has utility in organisms other than plants. It is therefore not appropriate to oblige the inventors to limit the present claims to their exemplified embodiment. See U.S. v. Telectronics, 8 U.S.P.Q.2d at 1223-1224; Spectra-Physics, 3 U.S.P.Q.2d at 1743.

E. Reconsideration and Withdrawal Requested

Because the specification provides detailed enablement of at least one embodiment of the claimed invention, and because the specification provides reasonable guidance as to the direction in which experimentation should proceed, and because any experimentation necessary to practice the claimed invention through-out its scope would not "require ingenuity beyond that to be expected of a person skilled of the art," applicants submit that this rejection is improper and request that it be reconsidered and withdrawn.

II. REJECTIONS UNDER 35 U.S.C. § 103(a)

A. Claims 39-44, 59, 60 and 72

Claims 39-44, 59, 60 and 72 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Sugita et al. ("Sugita"), in view of Aoyama et al ("Aoyama"). Applicants still disagree with the characterization of the present claims by the Patent Office as being "broadly drawn" towards a vector, when even the Patent Office recognizes no less than seven material limitations to the broadest claims. Applicants believe that the characterization of the claim as "broad" misrepresents the very specific nature of the invention, and the precision with which it is claimed, and unnecessarily complicates the analysis.

The Office Action states that Sugita teaches a method of

producing a transgenic plant or plant cell free of a marker gene, comprising introducing a vector into a plant cell "wherein said vector comprises a gene of interest, a marker gene, and a removable DNA element, which is flanked by recombination sites that are recognized by the recombinase, and the sites are oriented in the same direction." Office Action at 8. The Patent Office has deemed it prima facie obvious to combine this asserted teaching with the teaching of the GVG induction system in Aoyama. Office Action at 9. The Patent Office finds motivation for this combination in the citation of the "glucocorticoid system promoter" by Sugita. Id.

1. The legal standard to be applied

Applicants respectfully submit that this rejection is unwarranted. "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination or other modification." In re Lintner, 173 USPQ 560,562 (C.C.P.A. 1972); MPEP §706.02(j) ("the initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done.") As a matter of law, an obviousness determination requires consideration of

both the claimed invention and the prior art in their entireties:

> Analysis begins with a key legal question - what is the invention claimed? Courts [and the Patent and Trademark Office] are required to view the claimed invention as a whole. 35 U.S.C. § 103.
>
> * * *
>
> Among legal standards for determining scope and content of the prior art, for example, are: a prior patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit, [citations omitted].

Panduit Corp. v. Dennison Mfg. Co., 1 U.S.P.Q. 1593, 1597 (Fed. Cir. 1987) (emphases original). As explained below, the Patent Office has failed to apply these standards.

2. Failure to establish a prima facie case

The Office Action also fails to establish a case of prima facie obviousness. In order to establish a case of prima facie obviousness, the Patent Office must show 1) that there was a suggestion or motivation in the prior art to modify or to combine reference teachings, 2) that there was a reasonable expectation of success and 3) that the prior art teaches or suggests all of the claim limitations. MPEP § 706.02(j) In making the rejection, the Examiner can not use his or her own opinion to make up for the lack of any prior art evidence that supports the obviousness analysis. In re Jones, 21 USPQ 1941, 1944 (Fed. Cir. 1992) ("Conspicuously missing from this record is any *evidence*,

other than the PTO's speculation (if it can be called evidence) that one of ordinary skill in the herbicidal art would have been motivated to make the modifications of the prior art salts necessary to arrive at the claimed [compound]").

Applicants submit that the Patent Office has not made out a case for the prima facie obviousness of the claimed invention, and even assuming that such a case were established, there are substantial secondary indicia of non-obviousness that show the non-obvious nature of the claimed invention.

The claims at their broadest read:

> 39. A vector comprising a gene of interest, **a gene encoding a transcription factor**, a marker gene, an inducible gene encoding a recombinase, and two recombination sites, wherein said recombination sites **flank said gene encoding a transcription factor**, said marker gene, and said inducible gene.

(Independent claims 59 and 72 incorporate the limitations of claim 39). This language must be the touchstone for the obviousness analysis. Panduit, supra.

a. Insufficient showing of motivation to combine

The Patent Office finds motivation to combine Sugita with Aoyama in the mention by Sugita of a "glucocorticoid system promoter." Office Action at 9. This does not provide sufficient motivation to combine the references.

The Federal Circuit recently emphasized the criticality of

the motivation element in the obviousness analysis, stating

> "[o]ur caselaw makes clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references."

Ecolochem, Inc. v. Southern California Edison Co., 56 U.S.P.Q.2d 1065, 1073 (Fed. Cir. 2000). In order to prevent the use of hindsight, the Federal Circuit

> "requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed."

In re Rouffet, 47 U.S.P.Q.2d 1453, 1457-58, accord Ecolochem, 56 U.S.P.Q.2d at 1076. The rigorous application of the motivation element "stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness." In re Rouffet, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998).

All Sugita does is mention a glucocorticoid system promoter in a long list of inducible promoter systems. There still remains nothing in the combined references that would lead a person of ordinary skill in the art to select that particular promoter from among all of those listed, for use in combination with the other elements of the claimed methods, to achieve a

vector system that can function in any organism, with any marker. The Patent Office must explain "the specific understanding or principle with the knowledge of a skilled artisan that would motivate one with no knowledge of [the] invention to make the combination." In re Rouffet, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998). "When prior art references require selective combination ... to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself." Interconnect Planning Corp. v. Feil, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). Absent such specifics, the inference is that the examiner selected the references with the aid of impermissible hindsight. Rouffet, 47 U.S.P.Q.2d at 1458.

As the Federal Circuit has stated, "[t]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984). The prior art gives no suggestion of the desirability (not possibility) of making the specific modifications suggested by the Patent Office.

The broadest claims recite a "transcription factor," not a "glucocorticoid system promoter." Citation to a "glucocorticoid system promoter" does not suggest the use of transcription factors generally. The present claims recite "a marker," and the

methods are not limited to use in plants. Sugita, in contrast, teaches a system using a very specific kind of marker - a morphological abnormality gene, that can only be used in plants. Sugita repeatedly refers to the specific use of this kind of marker, and its advantageous use in the disclosed vector system. See, e.g., Sugita, et al., col. 3, lines 5-7 ("the object of the present invention can be accomplished by constructing a vector using a morphological abnormality gene as a selectable marker gene ..."); col. 3, line 38 ("Any of these [morphological abnormality] genes can be used in the present invention."); col. 7, lines 21-28 ("Accordingly, if the vector is constructed using this [morphological abnormality] gene ..." etc.); col. 7, lines 47-67 ("since the disappearance of the function of this selectable marker gene, namely the morphological abnormality induction gene, can be visually detected ..." etc.). Nowhere does Sugita refer to, or infer, the use of any other kind of marker gene. Sugita, in fact, points out in the Background the disadvantages of using other kinds of markers. See col. 1, lines 46-53. The Sugita reference, therefore, narrowly teaches a single kind of marker-excision system, which will only function in plants, and furthermore will only function in plants that regenerate via the organogenesis pathway (i.e., on plants that require the cytokinins produced by the morphological abnormality

genes to regenerate). Sugita, combined with Aoyama, provides no motivation to modify the vectors disclosed therein to employ any kind of marker other than a morphological abnormality gene (rather, the combination teaches away from the use of other markers). Applying the motivation element "rigorously," as is required, it is apparent that the combination and modification of references suggested by the Patent Office could only have been suggested by the impermissible use of hindsight. Rouffet, 47 U.S.P.Q.2d at 1453.

Considering the claims as a whole, the prior art does not teach or suggest the desirability of the particular modifications suggested by the Patent Office. Panduit Corp, 1 U.S.P.Q. at 1597("Analysis begins with a key legal question - what is the invention claimed? Courts [and the Patent and Trademark Office] are required to view the claimed invention as a whole. 35 U.S.C. § 103.") There is therefore insufficient motivation to make the suggested modification, and the first element of a case of prima facie obviousness is lacking.

b. No teaching or suggestion of all claim elements

Applicants respectfully disagree with the characterization of the teachings of the Sugita reference in the Office Action. As explained above, Sugita does not teach a system employing a "transcription factor" or "a marker," which is what the present

claims recite. Rather, Sugita teaches a system using a very specific kind of marker - a morphological abnormality gene -- and at most makes passing reference to a "glucocorticoid system promoter," which may or may not involve a transcription factor, and in any event does not suggest the use of transcription factors in general. Also, Sugita, either alone or in combination with Aoyama, does not teach or suggest vectors for use in organisms other than plants; the "vector" taught by Sugita is not the same as the "vector" of the present claims. Thus all of the elements of the claimed invention are not taught or suggested by the combination of Sugita with Aoyama. C.f., MPEP, § 706.02(j) ("To establish a *prima facie* case of obviousness ... the prior art reference (or references when combined) must teach or suggest all the claim limitations.") The third element of a case of prima facie obviousness is thus lacking.

c. Secondary indicia of non-obviousness

The non-obviousness of the claimed invention over the cited combination is further shown by other advantages of the present method that are not achieved with the system of Sugita, as modified with the teaching of Aoyama. For example, as discussed in the previous Response, with the present system it is possible to achieve excision in germ-line cells, thereby permitting transmission of the "excised" phenotype to subsequent

generations. In the prior art excision was only carried out in somatic cells, and there is no indication, or reasonable expectation, that the Sugita system (as modified by the teachings of Aoyama), would effectively cause excision in the deep L2 layers of cells from which germ-line cells arise. Additionally, in the plant embodiment, any standard regeneration technique (such as, e.g., somatic embryogenesis) can be used to obtain whole transgenic plants. These advantages are not present in the Sugita system. Also, the present system can be used to activate a silent gene, by the removal of a blocking sequence, or "stuffer," situated between said gene and its promoter. See Specification at page 6, lines 18-23. This advantage is not even hinted at in the cited combination of references.

The long-felt but unmet need in the art for a system such as that of the present claims further shows the non-obvious nature of the present invention - the PCT application corresponding to the cited Sugita U.S. patent was published in 1997, as was the Aoyama reference, yet in the three years leading up to the filing of the present application, no person skilled in the art was led to make the combinations and modifications to the art that are here suggested by the Patent Office. Such secondary indicia of non-obviousness further demonstrate that the present invention is not obvious over the prior art. In re Wagner et al., 152

U.S.P.Q. 552 (C.C.P.A. 1967)(Subjective opinions are of little weight against contrary evidence).

In view of the foregoing, applicants submit that the Patent Office has failed to consider the claims as a whole, and thus has failed to give credit to the unique combinations of the present invention, and their advantages over the prior art. The Patent Office also has failed to establish at least two of the three elements of a case of prima facie obviousness. Applicants respectfully submit that the rejection is misplaced, and request that it be reconsidered and withdrawn.

B. Rejection Of Claim 45

The Patent Office also has rejected claim 45 as being obvious over Sugita, in view of Aoyama, and further in view of Albert, et al. The Sugita and Aoyama references are applied as above. The Albert et al. reference is characterized as teaching mutant lox sites, and thus does nothing to overcome the basic deficiencies of the Sugita and Aoyama references that are discussed above. Thus, this combination of references can not, for the reasons discussed above, render the present claims obvious. Applicants request that the rejection be considered and withdrawn.

CONCLUSION

In view of the forgoing amendments and remarks, Applicants

submit that the claims are in condition for allowance, and requests withdrawal of all pending rejections and a favorable action on the claims.

Respectfully submitted,

By 

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